

REVIEW

Non-invasive Carotid Artery Imaging to Identify the Vulnerable Plaque: Current Status and Future Goals

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WHAT THIS PAPER ADDS

Characteristics of the carotid plaque in patients with carotid stenosis can identify those patients with relatively higher risk for stroke and help select patients who may benefit from intervention over medical treatment alone or vice versa. This review discusses the current role of two-dimensional and three-dimensional ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography in defining carotid plaque characteristics and in informing clinical practice. Most of these non-invasive imaging techniques have been discussed as single entity techniques. This paper puts the relative strengths and weaknesses of the different technical options in perspective in relation to clinical applicability.

Background: The current clinical practise to determine if a patient should undergo carotid intervention to prevent stroke is to determine the clinical features combined with degree of carotid stenosis. However, this does not accurately determine the individual patient's risk for future stroke. A thin fibrous cap, a large lipid core, high macrophage count, and intraplaque haemorrhage have all been identified as markers of the so-called "vulnerable" plaque being related to a higher stroke risk. There is a need to assess the accuracy of in vivo imaging to identify vulnerable plaque characteristics, thereby enabling in vivo risk stratification to guide clinical decision-making.

Methods: The aim of this topical review is to assess the roles of currently available imaging modalities that are applied in clinical practice and those experimental techniques that are close to clinical translation in defining carotid plaque characteristics and in informing clinical practice.

Results: Ultrasound is a low cost and ready available low-risk tool, but it lacks the accuracy to reliably detect individual plaque components and characteristics. Computed tomography is considered to be the best imaging technique to identify calcification in the carotid plaque. Magnetic resonance imaging (MRI) can identify most described plaque characteristics with moderate to good agreement. Positron emission tomography allows assessment of specific metabolic functions with tracers labelled with positron emitting radio-isotopes, but limited spatial resolution makes anatomic precision imprecise.

Conclusion: MRI has demonstrated the most potential, with good sensitivity and specificity for most plaque characteristics. However, currently there is no single imaging modality that can reliably identify the vulnerable plaque in relation to development of future stroke.

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Article history: Received 4 March 2015, Accepted 19 June 2015, Available online 19 August 2015

Keywords: Carotid artery, Non-invasive imaging, Vulnerable plaque

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<http://dx.doi.org/10.1016/j.ejvs.2015.06.113>

INTRODUCTION

Cerebral embolism from atherosclerotic carotid plaque remains an important pathophysiological mechanism of ipsilateral stroke, and carotid endarterectomy (CEA) in recently

symptomatic patients with a high-grade carotid artery stenosis significantly reduces the (recurrent) stroke risk.

The principle indication for carotid revascularisation is based on symptomatic status, timing, and degree of ipsilateral carotid artery stenosis. In symptomatic patients, with for example a single ocular symptom and smooth 70% carotid stenosis, the risk for recurrent stroke may be very low, and in these patients the benefit of revascularisation may be marginal. Alternatively, in asymptomatic patients the indication for revascularisation still remains a matter of debate, and current UK guidelines generally advocate a conservative approach in these patients, unless part of a clinical trial.¹ Overall in asymptomatic males, younger than 75 years, CEA compared with best medical treatment (BMT) significantly reduces the 10-year stroke risk.² However, based on clinical patient characteristics, selected subgroups of patients with asymptomatic carotid stenosis may benefit from carotid revascularisation. Increased systolic blood pressure, raised serum creatinine, smoking history, and a history of contralateral transient ischaemic attacks have been associated with an increased natural risk of ipsilateral cerebrovascular or retinal ischemic events.³ However, these parameters are insufficient to fully balance the natural risk with procedural risk and additional anatomical and vessel wall-specific parameters are needed to ultimately assess the individual patient risk for future stroke and related benefit of revascularisation.

Research in carotid imaging has focused on identifying characteristics that determine the “vulnerable” or unstable carotid plaque making the patient at “high risk for future ipsilateral stroke”.^{4,5} Several structural plaque characteristics are proposed that distinguish the “vulnerable” from the “non-vulnerable” plaque, which includes plaque ulceration, intraplaque haemorrhage (IPH), thin or ruptured fibrous cap (FC), lipid-rich necrotic core, and the presence of calcification.⁶ Inflammation may also play a role in the development and progression of disease as well as identifying the vulnerable plaque.⁷ A limitation of these studies on histological validation is the basis on post-endarterectomy specimens, and that they are mostly derived from symptomatic patients, with a relative long time interval between index event and CEA.⁸

Identifying features of the vulnerable plaque *in vivo* may help select patients who benefit from intervention over medical treatment alone or vice versa. A variety of conventional and advanced *in vivo* imaging modalities including two-dimensional (2D) or three-dimensional (3D) ultrasound (US), computed tomography (CT), high-resolution magnetic resonance imaging (HRMRI), and nuclear imaging techniques such as positron emission tomography (PET) have been applied to identify plaque characteristics. Each technique and modality has been applied in observational studies to identify features of the carotid plaque, but it is unclear whether these newer techniques can be translated to, and impact on, daily clinical care, leading ultimately to patient benefit.

This paper overviews the literature on currently available non-invasive imaging techniques to characterise the

vulnerable carotid plaque with histology as the gold standard, and summarises the challenges and needs for the development of next-generation imaging tools to be of help in future clinical decision-making (Tables 1 and 2).

ULTRASOUND

Current state

US is the modality of choice for initial evaluation and confirmation of carotid artery disease. US is used with high-resolution B-mode imaging alone or in combination with colour Doppler flow. US is a widely available, low cost and low-risk tool, which is well tolerated by patients and thus ideal for screening for the presence of the atherosclerotic plaque. A disadvantage is that it relies on the operator’s ability, and systemic haemodynamic and local anatomic factors, such as calcification and tortuosity of the carotid artery. Variable levels of interobserver agreement for Internal Carotid Artery Peak Systolic Velocity (ICA PSV) ranging from –25% to 43% between experienced technologists have been reported.⁹ However, in the UK the Society of Vascular Technologists promote internal audit with duplicate scanning between technicians to standardise reporting.

The use of the grey-scale median (GSM), a computerised measurement of plaque echogenicity, aims to differentiate echogenic carotid plaques (associated with a fibrocalcified content [stable appearance]) from echolucent plaques (with a thin FC, a higher lipid or haemorrhagic content [unstable appearance]). Although a low GSM, reflecting an echolucent (unstable) lesion, has been associated with an increased risk of cerebrovascular events,¹⁰ the use of different software and different applications for GSM measurement between research groups has resulted in a wide range of cut-off values for the definition of vulnerable plaque with no clear consensus or standardisation for routine practise.¹¹

Ulceration

A focal depression, causing an irregular surface, suggests plaque ulceration. The most widely used criteria to define plaque ulceration are the presence of a recess of at least 2 mm deep and 2 mm long, a well-defined wall at its base and an area of reversed flow at the level of the recess.¹² Ultrasound may vary significantly in sensitivity (33–75%) and specificity (33–92%) for determining plaque ulceration

Table 1. Non-invasive carotid imaging techniques and relevant needs for the future.

Techniques	Relevant needs for the future
Ultrasound (US)	3D ultrasound Contrast-enhanced ultrasound (CEUS)
Computed tomography (CT)	Automated removal of bone pixels Thin slice reconstructions 3D lumen geometry and shear stress
Magnetic resonance imaging (MRI)	3D SNAP protocol 7-Tesla MRI Automated segmentation techniques
Position emission tomography (PET)	Development of new tracers Coregistration PET/CT and PET/MRI

and in many cases may reflect the lack of familiarity in looking for this feature.^{13,14}

Intraplaque haemorrhage

Haemorrhage can be found at the adventitial side of the arterial wall as neovascularisation or intraluminal as a thrombus, and incorporated in the plaque.¹⁵ Causality is proposed by neovessel leakage or due to repeated plaque fissuring and formation of intraluminal thrombus that gets incorporated into the plaque.¹⁶ Presence of thrombus or intraplaque haemorrhage leads to an echolucent lesion on US that is similar to a fatty core. Sensitivity and specificity for detection of intraluminal thrombus using conventional 2D US are accurate in the range of 80–90% and 80–91% respectively.^{17,18} This is in contrast to GSM findings and intraplaque haemorrhage (IPH) histology ($r = -.31$ and $p = .07$).¹⁹

Neovascularisation itself can be detected by contrast-enhanced US. Plaques with a higher contrast agent enhancement showed a greater neovascularisation at histology (grade 2 vs. grade 1 contrast enhancement: median vasa vasorum density 3.24 mm^2 vs. 1.82 mm^2 , respectively, $p = .005$).²⁰

Fibrous cap

The fibrous cap (FC) appears as an echogenic structure that displays stronger echoes than the overall plaque and blood. Thickness of the FC can be determined with a 73% sensitivity and 67% specificity using stratified GSM measurements.²¹ Ultrasonic backscatter (IBS) was found to be lower in the thin FC compared with the thick FC.²²

Lipid-rich core

Lipid appears echolucent and similar to IPH on ultrasound. The presence of lipid necrosis contributes to a heterogeneous pattern of the plaque.²³ The Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study looked at the overarching feature of “juxtaluminal black area” to account for either IPH or a large fatty core, correlating this US feature with increased risk of stroke in an observational series.²⁴ The size of the lipid core seems critical for the stability of the plaque, the larger the pool the less stable the plaque.²⁵ Data on the ability to detect the lipid core are conflicting, using ultrasound ($p = .58$; $p = .031$) or computer-aided grey scale analysis ($r = .1$; $p = .37$).^{26,27}

Calcification

Calcification appears hyperechogenic and assessment has been described by the mean pixel value,²⁸ the GSM,¹⁰ and the pixel distribution.²⁶ All showed good correlation with histology, respectively $r = .8$, $p = .002$; $r = .30$, $p = .07$, and $p = .85$, $p = .001$. However, the studies were limited by a small sample size. Furthermore, acoustic shadowing of a heavily calcified plaque limits the assessment of severity of stenosis and other plaque characteristics.

Discussion and future directions

Ultrasound is a low-cost, low-risk tool, and well-tolerated by patients. However, it lacks the accuracy to reliably detect individual plaque components and characteristics.^{13,14,27} Specifically, IPH and a fatty core are both echolucent “black” areas. As is apparent from the above-named studies, several problems can be addressed: inter- and intraobserver variability, efficacy of standardised computerised assessments, and the limited assessment of a heavily calcified plaque due to acoustic shadowing. Research efforts are ongoing to overcome these limitations and to increase the clinical application of ultrasound.

3D imaging may show improved reproducibility and allows good visualisation of the luminal plaque surface and would therefore be of use in the detection of plaque ulceration. This technique detected carotid plaque ulceration more frequently than the 2D method (16.1% vs. 6.5% respectively).²⁹ As 3D US can capture all critical dimensions of the plaque, it has been used in volumetric measurements of the carotid plaque, showing observer variability in the range of 6–15%.^{30,31} Although 3D US seems promising, it remains a research tool as solid state 3D probes are in evolution and current techniques are time-consuming. Furthermore, data on the accuracy of 3D ultrasound plaque characterisation with histological validation are limited.^{29,32}

COMPUTED TOMOGRAPHY

Current state

CT angiography (CTA) is a validated tool for the non-invasive assessment of degree of carotid artery stenosis. Where ultrasound lacks the ability to image high bifurcation and tortuous vessels, CTA is able to image from the aortic arch to the brain parenchyma. However, the radiation dosage, the need for intravenous contrast, and calcification artefacts are acknowledged drawbacks. Hounsfield units (HU) are used to describe radiodensity on a quantitative scale.

Ulceration

The presence of a plaque ulcer on CTA is defined as an intimal defect with extension of contrast material beyond the lumen into the surrounding plaque. The use of a multidetector CTA (MDCTA) detects ulceration with moderate to good sensitivity (60–94%) and specificity (70–99%) when compared with histology.^{14,33}

Intraplaque haemorrhage

IPH is associated with very low HU values (–17 HU to 31 HU).^{32,33} MDCTA was able to detect plaques complicated with haemorrhage with good sensitivity (100%) and moderate to good specificity (64% and 70%).^{34,35} A further study showed good correlation of CTA with histology for large haemorrhages.³⁶

Table 2. The correlation of non-invasive carotid imaging techniques with histology.

	Year	Patients	Imaging	Histology	Sensitivity	Specificity	Correlation
Ultrasound — ulceration							
Comerota ^a	1990	109	Ulceration	Ulceration	47%	84%	NS
ECPSG	1995	270	Irregular plaque border	Ulceration	47%	63%	NS
Kardoulas	1996	36	Irregular plaque border	Ulceration	64%	68%	NS
Saba	2007	237	Ulceration	Ulceration	38%	92%	NS
Sitzer	1996	43	Ulceration	Ulceration	33%	76%	NS
			Ulceration/irregular plaque border	Ulceration	94%	33%	NS
Widder	1990	144	Irregular plaque border	Ulceration	75%	64%	NS
Ultrasound — intraplaque haemorrhage (IPH)							
Aburahma	1998	111	Irregular plaque border	IPH	81%	85%	NS
Gronholdt	2001	38	Grey-scale median (GSM)	% plaque haemorrhage	NS	NS	$r = -.31$ ($p = .06$)
Hatsukami	1994	24	Heterogenic and echolucent	Haemorrhage	53%	76%	NS
Kawasaki	2001	12	Backscatter index	Thrombus	80%	91%	NS
Lal	2006	42	PDA	% plaque haemorrhage	NS	NS	$r = .60$ ($p = .001$)
Noritomi	1997	15	Thrombus	Thrombus	90%	80%	NS
Widder	1990	144	Echolucent plaque	IPH	34%	36%	NS
Ultrasound — fibrous cap (FC)							
Sztajzel	2005	28	Low GSM values dominant at plaque surface	Thin FC	73%	67%	NS
Ultrasound — lipid-rich core (LRC)							
Lal	2006	42	Lipid core size	Lipid core size	NS	NS	$p = .58$ ($p = .031$)
Sztajzel	2005	28	Low GSM values dominant at plaque surface	Lipid core at luminal surface	84%	75%	NS
Tegos	2000	67	GSM	Necrotic core size	NS	NS	$r = .1$ ($p = .37$)
Ultrasound — calcification							
Gronholdt	2001	38	GSM	% plaque calcification	NS	NS	$r = .30$ ($p = .07$)
Lal	2006	42	PDA	% plaque calcification	NS	NS	$p = .85$ ($p < .0001$)
Computed tomography angiography (CTA) — ulceration							
Oliver	1999	13	Irregular lumen	Ulceration	50%	89%	NS
Saba	2007	109	Ulceration VR + axial	Ulceration	94%	99%	NS
Saba	2007	237	Ulceration	Ulceration	94%	99%	NS
Walker	2002	55	Ulceration	Ulceration	60%	74%	NS
Wintermark	2008	8	Ulceration	Ulceration	87%	99%	NS
CTA — IPH							
Ajduk	2009	31	HU	IPH	100%	64%	NS
Ajduk	2013	50	HU	IPH	100%	74%	NS
Gronholdt	2001	38	HU	% plaque haemorrhage	NS	NS	$r = -.1$ ($p = .57$)
Oliver	1999	13	Hypodense	Lipid/haemorrhage	94%	86%	NS
Wintermark	2008	8	Large haemorrhage	Large haemorrhage	62%	99%	NS
CTA — FC							
Wintermark	2008	8	HU	FC thickness	NS	NS	$r^2 = .77$ ($p < .001$)
CTA — LRC							
De Weert	2006	15	HU	Lipid core size	NS	NS	$r^2 = .24$ ($p < .001$)
				Lipid core size after excluding calcium			$r^2 = .81$ ($p < .001$)
Wintermark	2008	8	Lipid core	Lipid core	76%	74%	NS
CTA — calcification							
Das	2009	30	HU	Calcified plaques	NS	NS	$r = .95$
Gronholdt	2001	38	HU	% Calcification	NS	NS	$r = .34$ ($p = .04$)
De Weert	2006	15	HU	Calcification	NS	NS	$r^2 = .74$ ($p < .001$)
Wintermark	2008	8	Large calcifications	Large calcifications	100%	100%	NS
Magnetic resonance imaging (MRI) — ulceration							
Yu	2009	32	Ulceration	Ulceration	80%	82%	NS
MRI — IPH							
Albuquerque	2007	42		IPH	96%	96%	NS
Bitar	2008	8		IPH	97%	84%	NS

Table 2-continued

	Year	Patients	Imaging	Histology	Sensitivity	Specificity	Correlation
Cai	2002	60		IPH type VI	82%	91%	NS
Chu	2004	27		IPH	90%	74%	NS
Moody	2003	63		IPH type VI	84%	84%	NS
Puppini	2006	19		IPH alone	92%	100%	NS
Qiao	2011	8		IPH	79%	87%	NS
Saam	2005	40		IPH all areas	82%	77%	NS
				IPH areas > 2 mm ²	87%	84%	NS
MRI — FC							
Cai	2002	60		FC type IV/V	84%	90%	NS
				FC type VI	82%	91%	NS
Hatsukami	2000	22		FC rupture	89%	96%	NS
Mitsumori	2003	18		Unstable FC	81%	90%	NS
MRI — LRC							
Cappendijk	2008	50		LRC single sequence	77–100%	71–87%	NS
				LRC multisequence	82–100%	69–86%	NS
Yuan	2001	18		LRC alone	98%	100%	NS
Saam	2005	40		LRC all areas	92%	65%	NS
				LRC all areas > 2 mm ²	95%	76%	NS
Puppini	2006	19		LRC alone	92%	95%	NS
Young	2010	19		LRC	86%	40%	NS
MRI — calcification							
Cai	2002	60		Calcification Type VII	80%	94%	NS
Saam	2005	40		Calcification all areas	76%	86%	NS
				Calcification areas > 2 mm ²	84%	91%	NS
Puppini	2006	19		Calcification	80%	94%	NS
PET — inflammation							
Tawakol	2006	17	¹⁸ F-FDG	CD 68	NS	NS	$r = .7 (p < .0001)$
Graebe	2009	10	¹⁸ F-FDG	CD 68	NS	NS	$r = .71 (p = .02)$
Menezes	2011	21	¹⁸ F-FDG	CD 68	NS	NS	$r = .71 (p = .02)$
				MMP-9	NS	NS	

^a The complete reference citations from the table can be found in [Appendix 1](#).

Fibrous cap

An intact FC is believed to be associated with low-risk plaque rupture, whereas a thin or fissured plaque is associated with high-risk plaque rupture. FC thickness may be measurable with a good correlation to histology,³⁶ and MDCTA observed an association between fissured FC and cerebrovascular symptoms.³⁷ However this study did not incorporate a histological analysis.

Lipid-rich core

A lipid core can be identifiable as hypodense region, with a median tissue density ranging from 25 HU to 32.6 HU.^{36,38} In vivo MDCT may assess good correlations of a large lipid core with histology. However, findings were limited to mildly calcified plaques.³⁸

Calcification

CTA is a sensitive technique in the detection of calcification, which appears as a high-density structure in the plaque. The presence of calcification and quantification of calcification can be reliably detected with MDCT. A lower content of calcification was associated with a greater prevalence of neurological symptoms.³⁹

Discussion and future directions

CT is considered to be the best imaging technique to identify calcification in the carotid plaque.³⁹ However, significant overlap in HU values between different components and the presence of calcification artefact limit its use in plaque analysis. Removal of bone and calcification pixels could potentially be a solution, but this is a time-consuming process and therefore exceeds practical limits in routine clinical work flow. Therefore, a program for automated removal of bone pixels from CTA data sets has been proposed.⁴⁰

In addition to plaque morphology and severity of stenosis, MDCT has the ability to quantify plaque volume, with a moderate interobserver variability.⁴¹ Furthermore, plaque volume assessed by MDCT was correlated with severity of stenosis and cardiovascular risk factors.⁴²

There is increasing evidence that high shear stress plays an important role in the enhancement of plaque vulnerability.⁴³ However, little is known about the exact pathophysiological mechanism of shear stress in plaque progression. MDCTA 3D lumen geometry assessment may in the future contribute to the knowledge of various haemodynamic factors, such as sheared stress.⁴⁴

MAGNETIC RESONANCE IMAGING

Current state

Because of its high soft-tissue contrast, high in-plane resolution, and high reproducibility, MRI has shown great potential in atherosclerotic plaque imaging with good sensitivity and specificity. Several human in vivo studies have shown the ability to detect vulnerable plaque characteristics on 1.5-Tesla MRI, whereas the diagnostic accuracy of 3-Tesla and 7-Tesla MRI in patients with high-grade stenosis is currently under investigation.^{45,46} Important disadvantages of MRI include its relative low availability and long procedure time. Furthermore, with the use of a clinical 1.5-Tesla scanner, it still remains a challenge to distinguish different intraplaque tissues from each other because of an inferior signal-to-noise ratio than scanners using a higher field magnet.

Ulceration

MRI can detect ulceration with moderate sensitivity using 3D time-of-flight (TOF), T1, proton density, T2, and contrast-enhanced T1 sequences,⁴⁷ where it appears as a surface disruption on all contrast weightings. Adding longitudinal black-blood MR angiography increases the sensitivity and specificity of MRI to identify ulceration to 80% and 70% respectively.⁴⁸

Intraplaque haemorrhage

MRI is of clinical value in detecting IPH and one of the most investigated plaque components in MRI analysis. IPH can be detected with a sensitivity of 82–97% and specificity of 74–100%.^{45,49} According to the age of thrombus, IPH appears hyperintense on T1-weighted (T1W) and TOF images and hypointense on T2-weighted (T2W) and proton density weighted images (fresh thrombus), hyperintense on all contrast weightings (recent thrombus) or hypointense on all contrast weightings (organised thrombus).⁵⁰ It is hard to distinguish IPH from a lipid-rich core (LRC) as the thrombus is often located in the necrotic core.

Fibrous cap

On MRI the FC appears as a juxtaluminal band, which is hypointense at TOF weightings and isointense at T1, T2, and proton density weightings. The absence of this band can indicate either a ruptured or a thin FC. Differentiation between the last two still remains a significant challenge.⁴⁵ However, a 3D multiple overlapping thin slab protocol may be capable of distinguishing the thick intact FC from the intact thin and ruptured FC.⁵⁰

Lipid-rich core

An LRC can be detected on MRI with a sensitivity ranging from 82% to 100% and a specificity ranging from 40% to 100%.^{49,51,52} On MRI, T1 sequences can identify an LRC, where it appears as a hyperintense area. Detection of an LRC slightly improves when IPH is not present.⁵²

Calcification

Calcification can be detected by MRI with a sensitivity of 76–84% and specificity of 86–94%. It appears hypointense on all contrast images.^{45,49} Area measurement of calcification as a percentage of the vessel wall may be underestimated using histology as the reference.⁵¹

Discussion and future directions

Currently, MRI seems to have the most potential to identify vulnerable plaque components, as it benefits from high soft-tissue contrast and a high in-plane resolution. The aforementioned studies show that MRI can identify most described plaque characteristics with moderate to good agreement.^{45,48,49,51,52} Despite sufficient evidence that MRI can provide useful information on plaque characteristics, there are potential barriers to its implementation as a routine risk stratification tool. Most importantly, its high cost and low availability, especially for 3-Tesla and 7-Tesla MRI.

Recently a 3D-based MRI technique has been proposed. This technique combines three 4-minute carotid plaque sequences (3D SNAP, T1W pre- and post contrast) in a short scanning time.^{53,54}

Furthermore, there is a strong interest and ongoing research in potential labelled biomarkers that target specific molecules present in the “vulnerable” atherosclerotic lesion. Molecular MRI can be performed using iron oxide particles (USPIO) or other contrast agents that enhance specific molecules or cells, such as elastin, fibrin, or vascular cell adhesion molecule-1 and are of potential in identifying the “vulnerable” carotid plaque.⁵⁵

As previous analyses revealed that patients with silent cerebral ischaemic events are of high risk of future stroke, another potential area for future research may focus on the correlation between carotid plaque characteristics and cerebral damage. Compared with 1.5-Tesla and 3-Tesla, 7-Tesla MRI has proven to better visualise cerebral microbleeds and micro-infarcts. In symptomatic patients with high-grade stenosis, cerebral micro-infarcts detected by 7-Tesla MRI were correlated with the total cerebrovascular burden in the ipsilateral hemisphere.⁵⁶

Currently, the atherosclerotic plaque features derived from MRI wall imaging data are manually processed. Consequently, this is subject to inter- and intra-observer variability and an overall time-consuming process. Automated segmentation techniques have been developed to overcome these drawbacks.⁴⁴

POSITION EMISSION TOMOGRAPHY

Current state

PET allows assessment of specific metabolic functions with tracers labelled with positron emitting radio-isotopes. ¹⁸Fludeoxyglucose (¹⁸FDG) is the most explored and established PET tracer for in vivo imaging of atherosclerosis. ¹⁸FDG PET can probe plaque inflammation in vulnerable plaques directly. The disadvantage of PET is its limited spatial resolution (3–5 mm), which makes anatomic assignment for FDG

uptake imprecise. This can be partially offset by coregistration of the PET images with CT or MRI acquired by hybrid scanner constructs, which are becoming more widely available (PET/CT and more recently PET/MRI). Non-specific uptake of tracer by surrounding tissues (e.g. FDG uptake in adjacent muscles and nodes) is also a hindrance.

Inflammation

A significant correlation was found between the FDG PET signal and macrophage staining from the corresponding histologic sections in 17 patients with severe carotid stenosis.⁵⁷ Several studies have reported on the association between FDG uptake and the risk of future events in both asymptomatic and symptomatic individuals.^{57,58} Furthermore, in recently symptomatic carotid stenosis FDG uptake in the ipsilateral carotid plaque was greater in patients with early recurrent stroke.⁵⁹

Plaque morphology

In 50 patients with symptomatic carotid stenosis the correlation between plaque ¹⁸FDG standard uptake values and CT/MRI findings (lipid rich necrotic core, vessel wall, and fibrous tissue volume) was weak.⁶⁰ The correlations between CT and MRI findings were moderate to strong. LRNC and calcifications were significantly larger on CT, whereas measurements of fibrous tissue were significantly larger on MRI.⁶⁰ Plaque calcification, which is generally suggested to confer stability to the plaque, has also been found inversely related to PET and histological biomarkers of inflammation.⁵⁸

Discussion and future directions

PET has the advantage over existing imaging techniques to target inflammation directly, using ¹⁸FDG as radioactive tracer.⁵⁷ Because of its limited spatial resolution, it lacks anatomic precision and should therefore be combined with CT or MRI images. It is however a versatile technique with the potential to study other pathophysiological processes underpinning plaque evolution directly.

Currently, other molecular PET tracers are being studied in humans, for example ⁶⁸Ga-labelled somatostatin receptor probes as an alternative marker of inflammation and ¹⁸F-sodium fluoride potentially for microcalcification, with some success. Tracers that probe lipid accumulation, proteolysis, neoangiogenesis, and thrombosis are also potentially promising. However, data are limited and only available from preclinical molecular imaging studies.⁶¹ To facilitate the translation of promising PET tracers into the clinic setting, the co-registration of PET images with CT or MRI is of importance. Co-registration of MRI might be of additional benefit over CT as it better visualises the vessel wall.

Further information about molecular processes in the carotid plaque can be obtained by use of single photon emission computed tomography (SPECT). SPECT is similar to PET in detecting gamma radiation, but has the disadvantage of a two to three times lower spatial resolution. Radio-labeled SPECT tracers that are available for specific plaque vulnerability include ^{99m}Tc-labelled oxidised low-density

lipoprotein (^{99m}Tc-LDL) accumulation and apoptosis (^{99m}Tc-annexin-V).⁶²

DISCUSSION

The current review summarises the current state and more importantly future directions in non-invasive imaging of vulnerable carotid plaque. US, CT, MRI, and PET are non-invasive imaging techniques that show promise for identifying vulnerable plaque characteristics beyond the degree of stenosis.

Although the aforementioned imaging parameters are promising, at present there is no single imaging technique that can clearly identify the vulnerable plaque. This is because (a) there is no single imaging modality that can detect all vulnerable plaque features, (b) plaque imaging is expensive, time-consuming, and requires a reviewer with advanced experience, and (c) prospective natural follow-up studies analysing the value of these imaging modalities for future cerebral events are limited. It is therefore important to realise that even if we could reliably identify ulceration, LRC, thin FC, and IPH as characteristics of the vulnerable plaque, at this stage there is not enough evidence that these patients indeed have a higher risk of stroke.

In order to provide more detailed morphological information about the carotid plaque, the more established imaging techniques, such as US, CT, and MRI need to be further improved. Furthermore, the development of functional molecular imaging techniques (PET and SPECT) and 3D US hold promise for the future.^{29,57} In addition to the non-invasive imaging techniques covered in this review, several invasive techniques, such as optical coherence tomography, intravascular ultrasound (IVUS), or combined IVUS with near infrared spectroscopy, are areas of ongoing plaque imaging research, but were beyond the scope of the current review. Furthermore, due to the large amount of studies, it was not feasible to report one parameter that describes the correlation between plaque imaging techniques and histology.

Comparison of potential imaging characteristics of the vulnerable plaque with histological analysis is essential to further develop these future techniques. Application of plaque imaging in ongoing or proposed prospective studies and multicentre trials in patients with asymptomatic and symptomatic carotid artery stenosis will tell us in the near future if and how we can guide treatment on an individual patient level.^{63–65}

CONCLUSION

Currently available non-invasive imaging modalities for atherosclerotic carotid plaque offer the potential to identify specific vulnerable plaque components. MRI has the most potential, with good sensitivity and specificity for most plaque characteristics. However, currently there is no single imaging modality that can reliably identify the vulnerable plaque in relation to development of future stroke.

CONFLICT OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejvs.2015.06.113>

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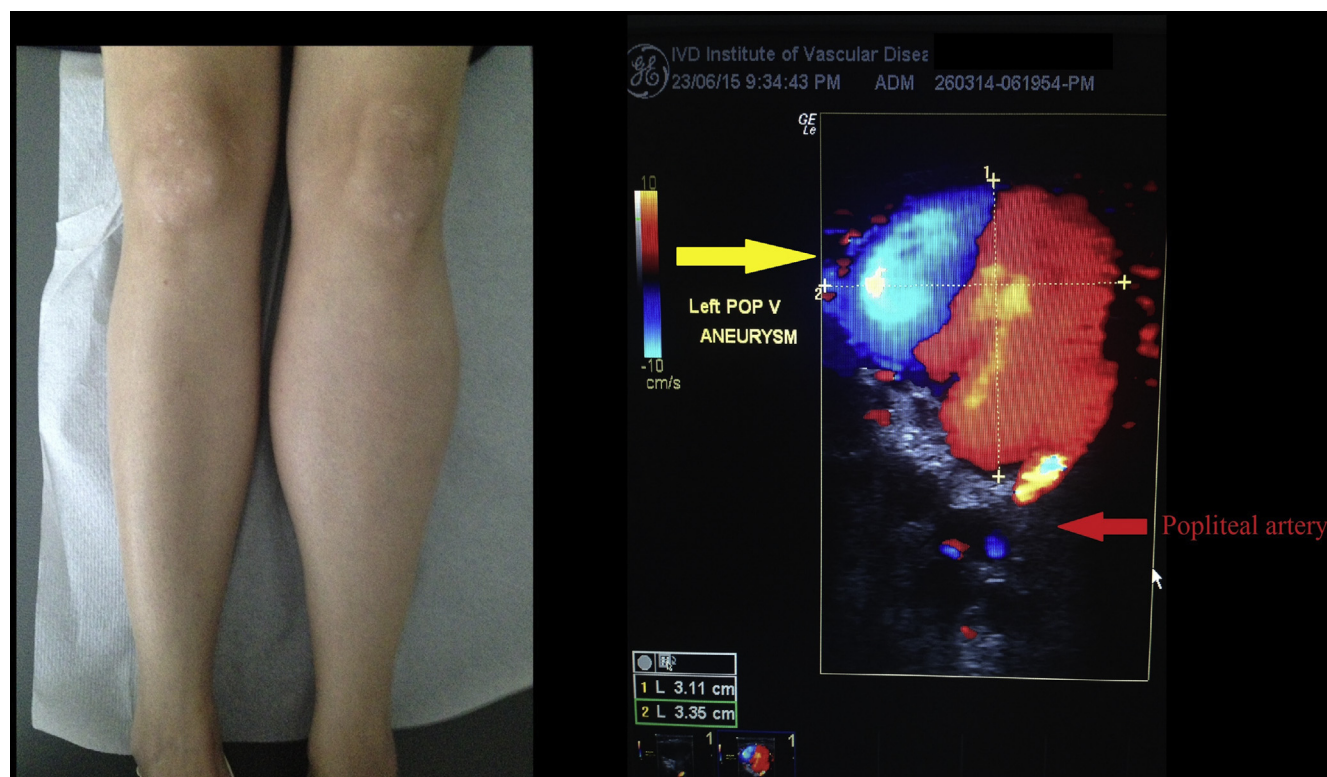
Eur J Vasc Endovasc Surg (2015) 50, 572

COUP D'OEIL

Popliteal Vein Aneurysm

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A 27-year-old female, 28 weeks pregnant (smoker with a previous caesarean section) presented with deteriorating left lower limb pitting oedema over the previous 2 weeks without varicose veins and no history of trauma in the limb. A colour flow ultrasound scan revealed a popliteal vein aneurysm 33.5×31.1 mm (yellow arrow) without thrombus along with dilated and incompetent superficial femoral and popliteal veins, a likely cause of the progressive swelling. A prophylactic dose of low-molecular-weight heparin and a knee-length elastic stocking were initiated for thromboembolic protection during pregnancy and the post-partum period. Prospects for future definite treatment will be discussed with the patient.

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<http://dx.doi.org/10.1016/j.ejvs.2015.07.030>